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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FISH & NEAVE IP GROUP
ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER
MEAH, MOHAMMAD Y

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/650,591	AFEYAN ET AL.	
	Examiner	Art Unit	
	Mohammad Meah	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *23 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25 and 28-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4- 25 and 28-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/24/06,7/5/05,9/27/05, 12/01/03*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

With preliminary amendment of this application, the applicant, on date 01/3/2006 elected with traverse adzyme comprising trypsin as catalytic domain linked via a linker with sp55 of TNFR1 as targeting domain reads on claims 1-2, 4-25 and 28-41 for examination.

Election/Restriction

During the preliminary amendment of this application, the applicant, on date 01/3/2006 elected with traverse adzyme comprising trypsin as catalytic domain linked via a linker with an sp55 of TNFR1 as targeting domain reads on claims 1-2, 4-25 and 28-41 for examination.

Claims 3, 26 –27 and 29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected Groups.

Applicants arguments of "restriction requirement is unwarranted because of claims are linked to generic claim 1 by a concept of "adzyme"- a fusion protein is noted and accepted that claim 1 is a linking claim linking the patentably distinct species of adzymes. However each of these species in the other claims is patentably distinct as illustrated in the office action of date 08/09/2005. The same argument is restated below again: Each catalytic domain of the fusion proteins encompassed by the instant claims is a patentably distinct protein having a different structure than the other catalytic domains encompassed by the instant claims. Similarly, each specific targeting domain

fusion encompassed by the instant claims is a patentably distinct protein having a different structure than the other targeting domains encompassed by the instant claims. N combinations of catalytic domain with N combinations of targeting domain will produce N^2 (such as 10 X10 = 100) patentably distinct adzymes having different structures. Furthermore each specific fusion protein will have distinct functional properties as well. As such each adzyme fusion protein is an independent invention.

Claim 1 link(s) inventions of claims 2-40.The restriction requirement of date 08/09/2005 for the linked inventions is subject to the nonallowance of the linking claim(s), claim 1. Many of the remaining claims link several but not - all distinct inventions as set forth in the claim. Upon allowance of any such linking claims the restriction will be withdrawn. Upon the indication of allowability of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise requiring all the limitations of the allowable linking claim(s) will be rejoined and fully examined for patentability in accordance with 37 CFR 1.104 Claims that require all the limitations of an allowable linking claim will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

Applicant(s) are advised that if any claim(s) including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction

requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. In re Ziegler, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Applicants further argue that there would be no undue burden on the examiner to examine claims directed to adzymes because they share "generic structure". This is not persuasive because while the search for each of these distinct groups would be overlapping it would not be coextensive. Art that applies for one serine protease and/or targeting domain protein may or may not be relevant to the others. Furthermore, it should be noted herein that while the examiner has attempted to search the generic claims herein using broad terms such as "fusion" "protease" etc, such searches are incomplete as many references that might disclose specific species often lack the generic language and therefore get missed if only generic language is used. In this case in particular this is highly problematic as the claims are so broad as to prevent the combination of generic terms with specific terms covering the entire scope of the genus. Therefore the restriction is maintained and made FINAL.

Priority

This application claims benefit of 60/406,517 08/27/2002 and claims benefit of 60/423,754 11/05/2002 and claims benefit of 60/430,001 11/27/2002

Claim Objections

Claim 19 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 2. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

35 U.S.C 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-13, 14-17, 31-32, 36 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention.

Claims 6-7, 16 - the recitation of the term "potency" or "potent" makes these claims confusing. What is "potency" ?

Claims 14-17- "said linker" lacks antecedent basis.

Claims 31-32- the recitation " abundant human serum protein" makes the claim indefinite. It is unclear what define "abundant".

Claim 36 – " said antagonist of said substrate competes said antagonist"- the antagonist is competing itself and therefore makes no sense.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4-25 & 28-41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of fusion protein of a protease conjugated optionally through a linker polypeptide with a genus of ligand binding domain or protein or peptide. The specification teaches the structure of only a few such fusion proteins or "adzymes". Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of adzyme. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 1-2, 4-25 & 28-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an adzyme or bifunctional fusion protein wherein trypsin is conjugated via a linker with sp55 of TNFR1 does not reasonably provide enablement for any fusion protein of any ligand binding domain or protein or peptide molecule with any protease

protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-2, 4-25 & 28-41 are so broad as to encompass any fusion protein of any protease and any ligand binding domain or protein or peptide. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number adzymes or fusion proteins that made via conjugation of broad class of protease conjugated through a linker polypeptide with broad class of ligand binding domain or protein or peptide. These claims drawn to fusion proteins having any structure. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only few fusion proteins of specific amino acid sequences.

Claims 6-13, 31 recite many kinetic properties (with specific kinetic parameters) of fusion proteins. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number adzymes or fusion proteins attached to these kinetic parameters. Since specific kinetic parameter will depend on the individual choice of protease linked with individual ligand binding domain or protein or peptide as well as on the type of conjugation with individual linker peptide, achievement of desired kinetic values for the

broad class of adzymes (made via conjugation of broad class of proteases conjugated through a linker polypeptide with broad class of ligand binding domain or protein or peptide) is highly unlikely. Specification disclose kinetic parameters for only two such adzymes.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass any fusion protein of any ligand binding domain or protein or peptide molecule or fragments or modified fragments thereof with any protease protein because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting adzyme activity; (B) the general tolerance of serine protease activity to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any residues for adzyme activity with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly include fusion protein of any ligand binding domain or protein or peptide conjugated with any protease or any protein having protease activity. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of adzyme activity, having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

CLAIM Rejection - 35 U.S.C 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 4, 14, 16-25, 28, 30-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Davis et al. (WO 00/64485). Davis et al. teach fusion proteins wherein enzymes (serine protease, chymotrypsin, metalloproteinase, etc) which catalyse degradation of a specific target are conjugated to binding partners wherein the binding partner is an ligand binding domain

or protein or peptide to the target with or without a linker and resulting fusion protein has greater (catalytic or more than one) activity than the unconjugated molecule. The chimeric protein of Davis et al. bind to the target and the antagonize/inhibit/degrade a wide variety of receptors and/or intermediary signaling molecules such as cytokines, EGF-like factors, etc. Davis et al. use the fusion protein as a pharmaceutical composition wherein the targeted enzyme is protease (trypsin, chymotrypsin) and use the pharmaceutical composition for autoimmune disease, infectous diseases , cancer, etc.

Claims 1-2, 4, 18-21, 30-34 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Holvoet et al. (JBC1991, vol.266, pp 19717-19724).

Holvoet et al. teaches (page I paragraph I and 2) fusion proteins of plasminogen activator (Urokinase – a serine protease) fused with a fibrin-specific antibody (, a polypeptide, variable region Fv) molecule. The resulting fusion protein shows 2.5-fold increase of the fibrinolytic potency. This fusion protein target cells (in this case blood clot) than cleave plasminogen to release active plasmin (an enzyme) resulting plasmin in turn inhibit/digest extracellular signalling molecules, act on cytokine transforming growth factor or lyse clot.

Claims 1, 2, 4, 14, 16-25, 28, 30-40 are rejected under 35 U.S.C. 102(e) as being anticipated by Chen et al. (US 2003/0068792). Chen et al. teach fusion proteins wherein enzyme (beta lactamase, serine protease, protease that resistant to protease inhibitors and etc) conjugated with or without a linker to ligand binding domain or protein or peptide to the target

proteins such as kinases, lipases , and tumor or cancerous cells via with or without a linker wherein the resulting fusion protein binds to the target better than unconjugated enzyme. The fusion protein of Chen et al. bind to the target and then inhibit/degrade a wide variety of targets associate with variety of hormones, receptors and/or intermediary signaling molecules such as cytokines, EGF-like factors, etc. Chen et al. use the fusion protein as a pharmaceutical composition wherein the targeted enzyme is protease and use the pharmaceutical composition for autoimmune disease, infectious diseases, cancer, etc.

Claims 6-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Holvoet et al. (JBC1991, vol.266, pp 19717-19724) and Chen et al. (US 2003/0068792).

Holvoet et al. teaches (page I paragraph I and 2) fusion proteins of plasminogen activator where fibrin-specific antibody (variable region Fv) molecule is fused with single chain Urokinase (a serine protease). The resulting fusion protein shows 2.5-fold increase of the fibrinolytic potency. Although Holvoet et al. does not disclose all the specific kinetic properties of the instant claims, the fusion protein had a 2.5-13 fold increase of the fibrinolytic potency compared to unconjugated enzyme. Fusion protein of single chain Urokinase fusion to antibody had the following kinetic parameters: $Ka = 5.5 \times 10^{9}\ M^{-1}$ $Km = 12$ microM and $Kcat = 0.12 \times 10^{-6}\ M^{-1}/sec^{-1}$ for the fusion protein compare to $0.02 \times 10^{-6}\ M^{-1}/sec^{-1}$ for unconjugated enzyme. In view of the above characteristics of the fusion protein of Holvoet, a skilled artisan would expect that the fusion protein of Holvoet et al. would meet the kinetic parameters recited in claims 8, 10-13.

Chen et al. teach fusion proteins wherein enzyme (beta lactamase, serine protease, protease that resistant to protease inhibitors and etc) conjugated to ligand binding domain or protein or peptide immunoglobulin or fragment or antibody to the target proteins such as kinases, lipases , and tumor or cancerous cells via with or without a linker and the resulting fusion protein bind to the target better than unconjugated enzyme. The fusion protein of Chen et al. bind to the target and then inhibit/degrade a wide variety of targets associate with variety of hormones, receptors and/or intermediary signaling molecules such as cytokines, EGF-like factors, etc. Although Chen et al. does not disclose the specific kinetic properties, they teach fusion protein which bind to the target 10-10000 better than unconjugated enzyme without substantially losing the enzymatic activity of the unconjugated enzyme. In view of the above characteristics of the fusion protein of Chen, a skilled artisan would expect that the fusion protein of Chen et al. would meet the specified kinetic properties of the instant claims.

Since the office does not have facilities to test the characteristics of a prior fusion protein and reasonable basis exists for believing that the prior art fusion protein has all the recited characteristics, it is the burden of the applicant to show that the fusion protein of the prior art lack the characteristics.

Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 4-25, 28, 30-41 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2, 4-25, 30-41 of copending Application No.10792498. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 1 of instant application comprises an adzyme comprising protease as catalytic domain and claim 1 of copending application 10792498 comprises an adzyme comprising serine protease as catalytic domain. The remainder of these two claims is identical as are the dependent claims thereof. As such the claims of the instant application and those of the copending application differ only in the scope of protease within the claimed adzymes. Serine protease is sub species of protease. Therefore, claims 1-2, 4-25, 28, 30-41 herein are anticipated by claims 1-2, 4-25, 28, 30-41 of copending 10792498.

Claims 1-2, 4-25, 28-41 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 7-38, 40-46, 52-60, 66-104, 107-134 of copending Application No.10,650592. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 1 of instant application comprises an adzyme comprising protease as catalytic domain fused with a targeting domain, acts on a extracellular substrate polypeptide resulting the inhibition of receptor-mediated signaling activity of the substrate and claims 1-6 of copending application 10,650592 comprises an adzyme comprising any enzyme as catalytic domain, fused with a targeting moiety, acts on any substrate (claims 1, 3-4), or extracellular signaling substrate (claim 2) or any polypeptide or extracellular substrate polypeptide (5-6) and inhibit the substrate activity. Claim 1-6 of the copending application further differ in scope from the instant claims in that claim 1 of the copending application recites specific kinetic parameters of the adzyme, claim 3 of the copending application limits the substrate to a receptor, claim 4 of the copending application recites that the product produced by the action of the enzyme on the substrate is an antagonist of the substrate and claim 5 of the copending application recites that adzyme is resistant to cleavage by the catalytic domain. These additional limitations are recited in the instant application only in dependent claims. However, the specification of copending application 10/650592 discloses the following specific embodiments of adzymes within the scope of claims 1-6, 7-38, 40-46, 52-60, 66-104 and 107-134 therein which support the genera of adzymes recited in the claim of the copending application: prothombin/scFv αHa, trypsin/sp55. It would have been obvious to one of ordinary skill in the art to select these specific embodiments of genera of the copending application to practice the invention thereof. These adzymes anticipate the instant claims herein.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mohammad Younus Meah, PhD

Examiner, Art Unit 1652

Recombinant Enzymes, 3C31 Remsen Bld

400 Dulany Street, Alexandria, VA 22314

Telephone: 517-272-1261

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600